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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/051,013	10/09/1998	TIMOTHY H. BESTOR	48075-B-PCT	7512

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/051,013	BESTOR, TIMOTHY H.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 48-56 are pending in the application.

[2] Applicant's amendment to the claims, filed June 21, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed June 21, 2004, is acknowledged.

[4] Receipt of an application data sheet (ADS), filed June 21, 2004, is acknowledged.

[5] Receipt of a statement that the substitute sequence listing includes no new matter, filed June 21, 2004, is acknowledged.

[6] Applicant's arguments filed June 21, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Oath/Declaration

[8] In view of applicant's submission of an ADS listing the inventor's mailing address, the objection to the declaration as set forth in item [5] of the Office action mailed March 17, 2004 is withdrawn.

Claim Objections

[9] Claims 50-51 are objected to in the recitation of "LexA site" in line 3 of claim 50 and in the recitation of "LexA DNA site" in lines 2-3 of claim 51. While it is clear that applicants intend for the term "LexA site" or "LexA DNA site" to be interpreted as a "LexA binding site" in the interest of clarity, it is suggested that applicant maintain consistency in the claims by, for example, replacing "LexA site" in claim 50 and "LexA DNA site" in claim 51 with "LexA binding site."

[10] Claims 52-53 are objected to as being grammatically incorrect in the recitation of "and Spiroplasma DNA methyltransferase" and should be replaced with, for example, "and a Spiroplasma DNA methyltransferase." Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

[11] Claims 48-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 48 and 49 (claims 50-51 and 56 dependent therefrom) recite the limitation "the DNA binding region of LexA." There is insufficient antecedent basis for this limitation in the claims. Further, this term is confusing as what is methylated is a CpG sequence adjacent to a LexA operator within a polynucleotide sequence, not CpG sites adjacent to a DNA binding region of LexA. It is suggested that applicant clarify the meaning of the claims.

[b] Claims 52, 53 (claim 56 dependent therefrom), and 54-55 recite the limitation "the Lac operator sequence." There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 112, First Paragraph

[12] The written description rejection of newly added claims 48-56 under 35 USC 112, first paragraph, is maintained for the reasons of record as set forth in item [7] of the Office action mailed March 17, 2004 and for the reasons stated below.

[13] RESPONSE TO ARGUMENTS: Applicant argues the specification demonstrates possession of the genus of claimed chimeric proteins by actual reduction to practice and by describing the distinguishing identifying characteristics of members of the genus, namely their preference for methylation of specific target sequences. Applicant refers to portions of the specification that: 1) allegedly describe the genus of chimeric proteins, 2) allegedly provide experimental data demonstrating the ability of the chimeric proteins to preferentially methylate a CpG site near a LexA or LacI DNA binding site, and 3) allegedly provide protocols for producing the claimed genus of chimeric proteins. Applicant argues that based on the teachings of the specification, one of skill would have recognized that applicant was in possession of the claimed genus of chimeric proteins. Applicants' argument is not found persuasive.

The examiner maintains the position that the specification fails to describe the claimed genus of chimeric proteins and vectors encoding therefor. The claims are drawn to a genus of Spiroplasma DNA methyltransferase-LexA DNA binding protein

fusion proteins or a genus of Spiroplasma DNA methyltransferase-LacI DNA binding protein fusion proteins and vectors encoding therefor. In order for the respective protein to function, i.e., specifically methylate CpG sites adjacent to either a LexA or LacI operator DNA sequence, the specification discloses that it is necessary to reduce the DNA binding activity of the Spiroplasma DNA methyltransferase protein by selecting mutants that exhibit this reduced binding activity (see, e.g., page 39, lines 20-24 and page 40, lines 3-8 of the instant specification). However, as stated in a previous Office action, the specification fails to disclose the structure of even a single representative species of the modified Spiroplasma DNA methyltransferase protein or a DNA encoding therefor, which is undisputed by applicants. Rather than describing the structural features of the members of the claimed genus, applicant describes the genus by functional characteristics (e.g., pages 6 and 8-9 and Figures 6 and 11-14) and presents trial and error screening methods that are required to produce members of the genus of chimeric proteins (see Examples 1 and 3, pages 39-42 and 44-47, respectively, of the specification). In this case, the genus of chimeric proteins is described solely in terms of functional features coupled with a trial and error method for its making. Thus, the issue at hand is whether a written description of a claimed genus of chimeric proteins is adequate where the members of at least one necessary component of the chimeric protein are described only in terms of their functions and where the only means for finding such components is essentially by trial-and-error. MPEP § 2163 states, "[t]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is

no described or art-recognized correlation or relationship between the structure of the invention and its function." In this case, there is no evidence of record that would support an art-recognized correlation or relationship of the structure of Spiroplasma DNA methyltransferase protein to the desired function, i.e., attenuated DNA binding activity without loss of methyltransferase activity. As such, the specification fails to adequately describe the claimed genus of chimeric proteins and vectors encoding therefor.

Also, it is noted that the CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly, with the claimed genus of chimeric proteins, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus that distinguishes the protein species within the genus from other chimeric proteins such that one can visualize or recognize the identity of the members of the genus.

It should be emphasized that the mutation(s) in the Spiroplasma DNA methyltransferase protein moiety of the genus of chimeric proteins that result in the

protein having the desired characteristics, i.e., attenuated DNA binding activity, are an essential and critical feature of the claimed invention and because the genus encompasses any structural variant of Spiroplasma DNA methyltransferase protein having attenuated DNA binding activity, the structures of the Spiroplasma DNA methyltransferase protein moiety encompassed by the genus of chimeric proteins are widely variant. While the mutation(s) are essential or critical to the claimed invention, it is noted that the trial and error screening methods for identifying the desired chimeric proteins (see Examples 1 and 3, pages 39-42 and 44-47, respectively, of the specification) are highly unpredictable as evidenced by the specification, which states, "[i]t cannot be predicted as to which mutations might give the desired reduction in affinity for DNA, so random mutations are introduced and selection is applied to obtain mutants of the desired character" (page 40, lines 10-14). Also, the specification acknowledges that such random mutations may not generate a DNA encoding the desired chimeric protein (page 42, lines 4-7), suggesting that there is little expectation of success for generating the members of the claimed genus. Addressing inventions in an unpredictable art, MPEP 2163 states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" and "for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession." Thus, even assuming arguendo the specification disclosed a single representative species – which it does not – in view of

the widely variant species encompassed by the claimed genus, the specification would fail to describe all species encompassed by the genus.

[14] The enablement rejection of newly added claims 48-56 under 35 USC 112, first paragraph, is maintained for the reasons of record as set forth in item [8] of the Office action mailed March 17, 2004 and for the reasons stated below.

[15] RESPONSE TO ARGUMENTS: Applicant argues undue experimentation is not required to make and use all chimeric proteins encompassed by the scope of the claims because: 1) the specification combined with the knowledge in the art provides information regarding the components of the chimeric proteins as well as a correlation between the component proteins' structures and their functions; 2) the level of skill in the art of producing functional chimeric proteins was high; 3) the specification provides guidance such as examples of the claimed chimeric proteins. Applicants' argument is not found persuasive.

As written, the claims are so broad as to encompass all chimeric proteins comprising a Spiroplasma DNA methyltransferase protein and a LexA or a LacI DNA binding protein, wherein the Spiroplasma DNA methyltransferase protein specifically methylates CpG sites adjacent to the chimeric protein's respective DNA binding site and vectors encoding therefor. It should be noted that in order for the respective chimeric protein to function, i.e., specifically methylate CpG sites adjacent to either a LexA DNA binding region or a LacI DNA binding region, the specification discloses that it is necessary to reduce the DNA binding activity of the Spiroplasma DNA methyltransferase protein by selecting mutants that exhibit this reduced binding activity

(see, e.g., page 39, lines 20-24 and page 40, lines 3-8 of the instant specification). However, the specification fails to provide the guidance that is necessary to enable the claimed invention. While there is no dispute that sequences of naturally-occurring Spiroplasma DNA methyltransferase protein, LexA protein, and LacI protein and methods for fusing two known encoding nucleic acid sequences to generate a functional fusion protein were known in the art at the time of the invention, this is not sufficient to remedy the lack of guidance provided in the instant specification. Herein, the only guidance in the specification for making the claimed chimeric protein is admittedly unpredictable as evidenced by the disclosure that "[i]t cannot be predicted as to which mutations might give the desired reduction in affinity for DNA, so random mutations are introduced and selection is applied to obtain mutants of the desired character" (page 40, lines 10-14). Moreover, the specification acknowledges that such random mutations may not generate a DNA encoding the desired chimeric protein (page 42, lines 4-7). MPEP § 2164.02 states, "if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art." In this case, and particularly in view of the teachings of the specification admitting to the unpredictability in making the chimeric protein, one of skill in the art cannot readily anticipate the effect(s) of a change, i.e., mutation, within the components of the chimeric protein with an expectation of obtaining a chimeric protein having the desired biological characteristics. Such unpredictability is evidenced by the prior art. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been

surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability" (page 247). While methods of generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen for all chimeric proteins comprising a Spiroplasma DNA methyltransferase protein moiety having any number of modifications such that the chimeric protein has the ability to specifically methylate CpG sites adjacent to particular DNA binding sites. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the significant quantity of experimentation required to make the full scope of claimed chimeric proteins, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Conclusion

[16] Status of the claims:

Claims 48-56 are pending.

Claims 48-56 are rejected.

No claim is in condition for allowance.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652
07-07-04